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APPLICATION NUMBER: *60/539,068*
FILING DATE: *January 23, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US05/02462*

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV308275980US

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
RAFAEL	SHAPIRO	WILMINGTON, DELAWARE

Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

PROCESS FOR THE MANUFACTURE OF 2,3-DICHLOROPYRIDINE

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 17
☐ Drawing(s) *Number of Sheets* _____
☐ Application Date Sheet. See 37 CFR 1.76
☐ CD(s), Number _____
☑ Other (specify) FEE SHEET

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.
☐ A check or money order is enclosed to cover the filing fees.
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☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE Amount ($): $160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.
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Respectfully submitted,

SIGNATURE Linda D. Birch

TYPED or PRINTED NAME LINDA D. BIRCH

TELEPHONE (302) 992-4949

Date January 23, 2004

REGISTRATION NO. 38,719 *(if appropriate)*

Docket Number: BA9327USPRV

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) **160.00**

Complet if Known	
Application Number	UNKNOWN
Filing Date	JANUARY 23, 2004
First Named Inventor	Rafael Shapiro
Examiner Name	UNKNOWN
Art Unit	UNKNOWN
Attorney Docket No.	BA9327 US PRV

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☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

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Deposit Account Number: **04-1928**

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	160.00

SUBTOTAL (1) ($) **160.00**

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims		Fee from below	Fee Paid
Total Claims	-20** =		X	18	=
Independent Claims	- 3** =		X	86	=
Multiple Dependent ☐ YES				290.00	=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) **0.00**

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

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SUBTOTAL (3) ($) **0.00**

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Linda D. Birch	*Registration No. (Attorney/Agent)*	38,719	*Telephone*	(302) 992-4949
Signature	Linda D. Birch			*Date*	JANUARY 23, 2004

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TITLE

PROCESS FOR THE MANUFACTURE OF 2,3-DICHLOROPYRIDINE

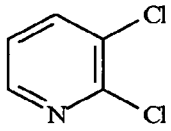
BACKGROUND OF THE INVENTION

A need exists for efficient and practical processes for the manufacture of 2,3-dichloropyridine. 2,3-Dichloropyridine is an important raw material for the preparation of crop protection agents, pharmaceuticals and other fine chemicals.

H. J. den Hertog, *et al., Recl. Trav. Chim. Pays-Bas*, **1950**, *69*, 673, report the preparation of 2,3-dichloropyridine from 3-amino-2-chloropyridine by the Gatterman reaction, in which copper powder was used as a catalyst. However, the usefulness of the reported method is severely limited with respect to low yield cited (i.e. 55%) and limited scale (less than 5 g).

SUMMARY OF THE INVENTION

This invention relates to a method (Method A) of preparing 2,3-dichloropyridine **1**,



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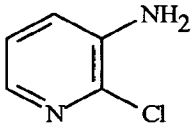
comprising the steps of:

(1) contacting a solution comprising 3-amino-2-chloropyridine **2**



2

with a first aqueous solution comprising hydrochloric acid to form 3-amino-2-chloropyridine hydrochloric acid salt;

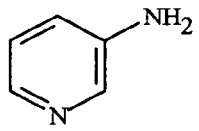
(2) contacting the 3-amino-2-chloropyridine hydrochloric acid salt with an aqueous solution comprising a nitrite salt to form a diazonium salt; and

(3) contacting the diazonium salt with an aqueous solution comprising a Cu(II) salt in the presence of a second aqueous solution comprising hydrochloric acid, optionally in the presence of an organic solvent, to form 2,3-dichloropyridine **1**.

This invention also relates to a method (Method B) of preparing 2,3-dichloropyridine **1**, comprising the steps of:

(a) contacting a solution comprising 3-aminopyridine **3**

2



3

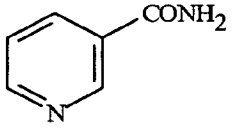
with aqueous hydrochloric acid and a chlorinating agent to form a mixture;

(b) isolating a solution comprising 3-amino-2-chloropyridine hydrochloric acid salt from the mixture; and

(c) using the solution comprising 3-amino-2-chloropyridine hydrochloric acid salt in Method A described above for the preparation of 2,3-dichloropyridine.

This invention also relates to a method (Method C) of preparing 2,3-dichloropyridine **1** comprising the steps of:

(i) contacting nicotinamide **4**



4

with a strong base and a halogenating agent in an aqueous solution at a temperature ranging from about –5 to about 20 °C to form a mixture comprising an *N*-halonicotinamide salt;

(ii) contacting the *N*-halonicotinamide salt mixture generated in step (i) with water and maintaining a resulting aqueous mixture at a temperature ranging from about 65 to about 100 °C;

(iii) isolating a solution comprising 3-aminopyridine hydrochloric acid salt from the aqueous mixture of step (ii); and

(iv) using the solution comprising 3-aminopyridine hydrochloric acid salt in Method B described above for the preparation of 2,3-dichloropyridine.

DETAILED DESCRIPTION OF THE INVENTION

Preferred methods of the present invention for the reasons of cost and ease of synthesis are:

Preferred 1. The method of Method A wherein the nitrite salt is sodium nitrite.

Preferred 2. The method of Method A wherein the Cu(II) salt is copper(II) chloride or copper (II) oxide.

Preferred 3. The method of Method A wherein

the nominal mole ratio of the nitrite salt to 3-amino-2-chloropyridine is about 0.95 to about 2.0;

the nominal mole ratio of the Cu(II) salt to 3-amino-2-chloropyridine is about 0.05 to about 2.0;

the nominal mole ratio of the hydrochloric acid in the first aqueous solution to 3-amino-2-chloropyridine is about 3 to about 10; and

the nominal mole ratio of the hydrochloric acid in the second aqueous solution to 3-amino-2-chloropyridine is about 0 to about 10.

Preferred 4. The method of Preferred 3 wherein

the nominal mole ratio of the nitrite salt to 3-amino-2-chloropyridine is about 0.95 to about 1.1;

the nominal mole ratio of the Cu(II) salt to 3-amino-2-chloropyridine is about 0.2 to about 0.6;

the nominal mole ratio of the hydrochloric acid in the first aqueous solution to 3-amino-2-chloropyridine is about 3 to about 6; and

the nominal mole ratio of the hydrochloric acid in the second aqueous solution to 3 amino-2-chloropyridine is about 1 to about 5.

Preferred 5. The method of Method A wherein

steps (1) and (2) are conducted at a temperature ranging from about –15 to about 20 °C; and

step (3) is conducted at a temperature ranging from about 30 to about 90 °C.

Preferred 6. The method of Preferred 5 wherein

the temperature of steps (1) and (2) range from about –10 to about 10 °C ; and

the temperature of step (3) ranges from about 50 to about 80 °C.

Preferred a. The method of Method B wherein the chlorinating agent is chlorine, an alkali metal hypochlorite or a mixture of hydrochloric acid and hydrogen peroxide.

Preferred b. The method of Preferred b wherein the chlorinating agent is chlorine or a mixture of hydrogen peroxide and hydrochloric acid.

Preferred c. The method of Method B wherein

the nominal mole ratio of hydrochloric acid to 3-aminopyridine is about 3 to about 20; and

the nominal mole ratio of the chlorinating agent to 3-aminopyridine is about 0.6 to about 1.5.

Preferred d. The method of Preferred c wherein

the nominal mole ratio of hydrochloric acid to 3-aminopyridine is about 5 to about 15; and

the nominal mole ratio of the chlorinating agent to 3-aminopyridine is about 0.8 to about 1.2.

Preferred e. The method of Method B wherein step (a) is conducted at a temperature ranging from about 0 to about 60 °C.

Preferred f. The method of Preferred e wherein the temperature of step (a) ranges from about 10 to about 35 °C.

Preferred i. The method of Method C wherein the strong base is an alkali metal hydroxide.

Preferred ii. The method of Preferred i wherein the alkali metal hydroxide is sodium hydroxide.

Preferred iii. The method of Method C wherein the halogenating agent is chlorine, bromine, or sodium hypochlorite.

Preferred iv. The method of Method C wherein

the nominal mole ratio of the strong base to nicotinamide is about 2 to about 5; and

the nominal mole ratio of the halogenating agent to nicotinamide is from about 0.8 to about 2.0.

Preferred v. The method of Preferred iv wherein

the nominal mole ratio of the strong base to nicotinamide is about 2 to about 3; and

the nominal mole ratio of the halogenating agent to nicotinamide is about 0.9 to about 1.1.

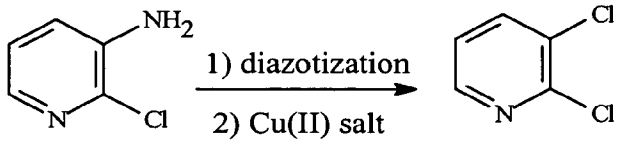
Preferred vi. The method of Method C wherein

the temperature of step (i) ranges from about 0 to about 10 °C; and

the temperature of step (ii) ranges from about 70 to about 95 °C.

According to Method A of the present invention as shown in Scheme 1, 2,3-dichloropyridine **1** is prepared by diazotization of 2-chloro-3-aminopyridine followed by decomposition of the diazonium salt in the presence of a Cu(II) salt.

Scheme 1



2 1

The diazonium salt can be prepared by reaction of 3-amino-2-chloropyridine with nitrous acid in an aqueous solution at a suitable temperature. The nitrous acid can be generated *in situ* from a nitrite salt and hydrochloric acid. Various nitrite salts can be used, such as sodium nitrite, potassium nitrite, calcium nitrite, or any alkali or alkali earth nitrite. A preferred nitrite salt is sodium nitrite for the reasons of cost and availability. For references on how to prepare diazonium salt see H. Zollinger, *Azo and Diazo Chemistry,* Wiley-Interscience, New York, 1961; S Patai, *The Chemistry of Diazonium and Diazo Groups,*

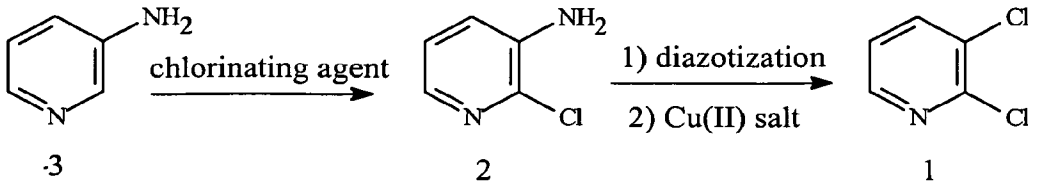
Wiley, New York, 1978, Chapers 8, 11 and 14; and H. Saunders and R.L.M. Allen, *Aromatic Diazo Compounds*, Third Edition, Edward Arnold, London, 1985. In the process of the present invention, a solution comprising 3-amino-2-chloropyridine **2** is contacted with a first aqueous solution comprising hydrochloric acid to form 3-amino-2-chloropyridine hydrochloric acid salt. The 3-amino-2-chloropyridine hydrochloric acid salt is then contacted with an aqueous solution comprising a nitrite salt to form a diazonium salt. Diazotization of the 3-amino-2-chloropyridine hydrochloric acid salt is preferably accomplished by adding aqueous sodium nitrite to a mixture of the 3-amino-2-chloropyridine in about 10% to about 37% aqueous hydrochloric acid. Additional preferreds for Method A are described above.

The diazonium salt is decomposed in the presence of a Cu(II) salt and hydrochloric acid to form 2,3-dichloropyridine. The Cu(II) salt can be, for example but not limitation, copper(II) acetate, copper(II) nitrate, copper(II) sulfate, copper(II) oxide (CuO), or copper(II) chloride ($CuCl_2$). Preferred Cu(II) salts are copper(II) oxide (CuO), copper(II) chloride ($CuCl_2$), or copper(II) chloride generated *in situ* from CuO and hydrochloric acid (HCl). The decomposition can be conducted in an aqueous solution, i.e. one-phase system, comprising preferably about 0 to about 10, more preferably about 1 to about 5, mole equivalent of about 10% to about 37% aqueous HCl, and preferably about 0.05 to about 2, more preferably about 0.2 to about 0.6 mol equivalent of Cu(II) salt at a temperature ranging from about 30 to about 90 °C. A preferred decomposition temperature is about 50 to about 80 °C. The decomposition can also be conducted in a two-phase system, comprising a suitable organic solvent and the aqueous solution of the one-phase system. The suitable organic solvent for the two-phase system can be, for example but not limitation, tetrahydrofuran, cyclohexane, ethyl acetate, *n*-chlorobutane, toluene, or benzene. The volume ratio of the organic phase and aqueous phase in the two-phase system can range from about 1:10 to about 10:1. The product, 2,3-dichloropyridine, in the two-phase system can be isolated by dilution of the reaction mass with water or aqueous, phase-separation, and concentration to dryness. The product of 2,3-dichloropyridine can also be isolated by crystallization followed by filtration. The crystallization can be achieved by partial concentration of the organic solution from the phase-separation, an optional solvent-exchange, and an optional addition of an "antisolvent" such as heptane or water. The isolated yield of 2,3-dichloropyridine (ca. 98% purity) can be about 90-95% starting from pure 3-amino-2-chloropyridine. The aqueous phase can be recycled directly into a subsequent decomposition batch, with optionally partial concentration, for the reuse of Cu(II) salt catalyst and excess hydrochloric acid.

According to Method B of this invention as shown in Scheme 2, 2,3-dichloropyridine **1** can be prepared by chlorination of 3-aminopyridine **3** followed by

diazotization of the resulting 2-chloro-3-aminopyridine intermediate and decomposition of the diazonium salt as described above in Method A.

Scheme 2



3 2 1

In the process of the present invention, a solution comprising 3-aminopyridine **3** is contacted with aqueous hydrochloric acid and a chlorinating agent to form a mixture. Chlorination of 3-aminopyridine **3** can be achieved by various suitable chlorinating agents, such as chlorine, alkali metal (such as lithium, sodium or potassium) hypochlorite, or a mixture of hydrochloric acid and hydrogen peroxide. Preferred chlorinating agents for Method B are described above. 3-Amino-2-chloropyridine **2** is known to be prepared from 3-aminopyridine by reacting the latter with hydrochloric acid and hydrogen peroxide at a temperature of 70-80 °C (O. von Schickh, A. Binz, and A. Schultz, *Chem. Ber.*, **1936**, *69*, 2593). However, this method easily provides over-chlorinated products (e.g. 3-amino-2,6-dichlorpyridine) because of the relatively high reaction temperature. This method was optimized by Yuan et al. (*Zhongguo Yiyao Gongye Zazhi*, **2000**, *31*, 420), to lower the reaction temperature to 20-30 °C and to reduce the amount of over-chlorinated product to 8 wt% by using 1 mol equivalent of 15 wt% hydrogen peroxide and concentrated aqueous HCl (ca. 37 wt%).

3-Amino-2-chloropyridine **2** is also known to be prepared from 3-aminopyridine by transition-metal catalyzed chlorination of 3-aminopyridine (Blank, et al., US 3,838,136). This method, while providing better yields on production scale than von Schickh's method described above, has the limitations that a hazardous material (chlorine) is required, the product is isolated as a solid in relatively impure form (ca. 87 wt%), and the metal catalysts are not easily recyclable and thus constitute potential waste-disposal issues. Purification of 3-amino-2-chloropyridine obtained by the method of Blank et al. from 2,6-dichloro-3-aminopyridine, i.e. the by-product, was described by K. Ieno in JP 09227522.

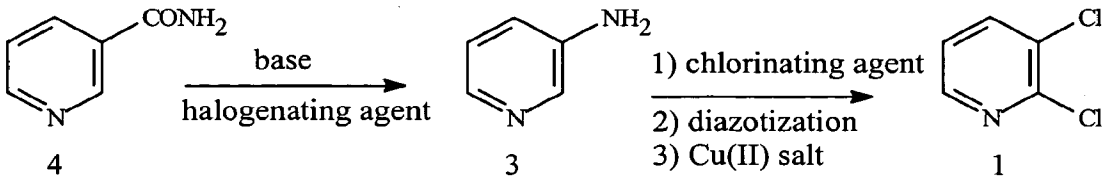
In a preferred embodiment of the present invention, a more selective chlorination method is used to produce higher quality 3-amino-2-chloropyridine from 3-aminopyridine by using a high strength hydrogen peroxide (about 20 to about 50 wt%), concentrated HCl, and a low temperature (about 10 to about 35 °C). This selective chlorination method can minimize over-chlorinated products (primarily 3-amino-2,6-dichloropyridine), even at a high conversion percentage of 3-aminopyridine. Furthermore, a modification of the Ieno's method allows for purification of 2-chloro-3-aminopyridine and continuation of the crude 2-

chloro-3-aminopyridine into the diazotization step without recourse to recrystallization and filtration.

The selective chlorination method described above can be carried out in the presence of preferably about 3 to about 20, more preferably about 5 to about 15, mol equivalents of concentrated aqueous hydrochloric acid to 3-aminopyridine and preferably about 0.6 to about 1.5, more preferably, about 0.8 to about 1.2 mol equivalents of hydrogen peroxide to 3-aminopyridine. The concentration of the concentrated aqueous hydrochloric acid can range from about 30 to about 37 wt%. A maximum HCl concentration is preferred in order to obtain an optimum reaction rate and selectivity in the chlorination step. The chlorination is accomplished by adding about 30 to about 50 wt% aqueous hydrogen peroxide at a temperature ranging from about 0 to about 60 °C over 1 to 8 hours to a mixture of 3-aminopyridine **3** and the concentrated hydrochloric acid. A preferred chlorination temperature is about 10 to about 35 °C for reasons of selectivity and reaction rate. A reaction yield of about 70-80% can be obtained at >90% conversion of 3-aminopyridine. In order to isolate the crude solution of 3-amino-2-chloropyridine hydrochloric acid salt from the mixture, the overchlorinated by-products can be removed by the modified Ieno method, i.e. selective extraction of the by-products with a non-water-miscible organic solvent such as diethyl ether, ethyl acetate, toluene, benzene or chlorobutane after partial neutralization of the reaction mixture to a pH of 1 to 3 with an inorganic base such as sodium hydroxide, potassium hydroxide, or sodium carbonate. The 3-amino-2-chloropyridine remaining in the aqueous solution can then be extracted with the same organic solvent or another suitable organic solvent after further neutralization of the aqueous solution to a pH of about 3 to 6. This procedure can leave most of the unconverted 3-aminopyridine in the aqueous waste. The organic extract containing the purified 3-amino-2-chloropyridine can be extracted with aqueous hydrochloric acid and the aqueous extract can be subsequently used in the diazotization reaction as described in Method A. Alternatively, the organic extract can be concentrated and the resulting crude 3-amino-2-chloropyridine can be further processed to 2,3-dichloropyridine as described above in Method A.

As shown in Scheme 3, the present invention relates to an efficient and concatenated process to prepare 2,3-dichloropyridine without having to isolate intermediate solids (Method C). The process involves Hofmann rearrangement of nicotinamide **4** to form 3-aminopyridine **3**, selective chlorination of 3-aminopyridine with a suitable chlorinating agent as described above in Method B, diazotization of the 2-chloro-3-aminopyridine intermediate, and decomposition of the diazonium salt with copper (II) salt as described above in Method A.

Scheme 3



Nicotinamide is a readily available and cost effective precursor to prepare 3-amino-2-chloropyridine and/or 2,3-dichloropyridine. Hofmann rearrangement of nicotinamide to form 3-aminopyridine can be achieved in the presence of a suitable halogenating agent and a strong base. The suitable halogenating agent can be, for example but not limitation, chlorine, bromine, hypochlorous acid, hypobromous acid, alkali metal (such as lithium, sodium or potassium) hypochlorite, alkali metal hypobromite, or benzyltrimethyl ammonium tribromide. Preferred halogenating agents of the present invention are chlorine, bromine, or sodium hypochlorite. The suitable strong base can be an alkali metal hydroxide. For Hofmann rearrangement references see *Org. Synthesis*, **1950**, *30*, 3; US 4,082,749; *Chemistry Letters*, **1989**, *3*, 463; and *Chem. Revs*, **1954**, *54*, 1083. Y. Ahmad and D. H. Hey (*J. Chem. Soc.*, **1954**, 4516) have described a procedure to convert nicotinamide to 3-amino-2-chloropyridine without having to isolate 3-aminopyridine intermediate.

Preferred for the process of the present invention is a modified Hofmann rearrangement involving *N*-halonicotinamide salt formed under feed-controlled conditions, wherein the amount of strong base used is higher than that typically employed in such rearrangements. The modified Hofmann rearrangement is carried out by co-feeding about 0.8 to about 2.0 equivalents of about 5-15 wt% halogenating agent in an aqueous solution and about 2.0 to about 5.0 equivalents of about 10-50% aqueous strong base to a 10 to 30 wt% nicotinamide aqueous mixture at a temperature between -5 and 20 °C and maintaining the pH of the reaction mixture higher than 10. The resulting solution of *N*-halonicotinamide salt is then added to 1 to 10 volumes of water in a second reactor over about 0.5 to 3 hours and the resulting aqueous mixture is maintained at about 65 to about 100 °C. Preferred strong base is alkali metal hydroxide. Preferred alkali metal hydroxide is sodium hydroxide, i.e. caustic. Also preferred is about 2 to about 3 equivalents of strong base to nicotinamide to minimize the formation of the by-product di(3-pyridyl)urea. Also preferred is about 0.9 to 1.1 equivalents of halogenating agent to nicotinamide. The modified Hofmann rearrangement can provide a very high reaction yield. The resulting mixture, comprising crude 3-aminopyridine, can be carried into the chlorination step as described above in Method B after isolation which can include acidification with an acid to a pH of about 1 to 5. To obtain an optimum rate and selectivity in the chlorination of 3-aminopyridine, which requires maximum HCl concentration, the acidified mixture can be concentrated to

approximately 10-30 wt% 3-aminopyridine and then added about 7 to 15 equivalents of gaseous HCl.

It is believed that one skilled in the art using the preceding description can utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative, and not limiting of the disclosure in any way whatsoever. Percentages are by weight except for where otherwise indicated. Quantitative HPLC of the product was performed using a Zorbax Eclipse XDB-C8® pre-packed chromatography column (reversed phase column manufactured by Agilent Technologies, Palo Alto, CA 94303) (3 μm particle size, 4.6 mm × 15 cm, eluent 15-95% acetonitrile / 0.05% TFA/water).

EXAMPLE 1

Preparation of 2,3-dichloropyridine

To a 300-mL sidearm flask was charged 12.8 g (0.10 mmol) of commercial 3-amino-2-chloropyridine, 30 mL of water, and 30 mL of 37% aqueous HCl. After the mixture was cooled to -8 °C (a slurry forms), a solution of 7.0 g (0.10 mol) of $NaNO_2$ in 14 mL of water was added over 30 minutes at -7 to -3 °C. The orange solution became a thin yellow suspension towards the halfway-point of the addition. After the addition, the mixture including the diazonium salt was transferred to a jacketed addition funnel at 0 °C. The diazonium salt mixture was added dropwise to a flask containing 20 mL of 37% aqueous HCl, 60 mL of *n*-BuCl, and 4.5 g of CuO at 55-62 °C under nitrogen.

The reaction mass was diluted with 100 mL of water and the *n*-BuCl layer was separated, washed with water, and concentrated to dryness to yield 13.8 g crude 2,3-dichloropyridine as a pale yellow solid (92% yield) with 98% purity.

EXAMPLE 2

Preparation of 3-amino-2-chloropyridine using hydrogen peroxide

3-Aminopyridine (30.0 g, 0.32 mole) was add to 300 mL of 37% aqueous HCl in a 1-L Morton flask with overhead stirring at about 30-35 °C. After the mixture was cooled to about 10 °C, 23 g (0.34 mol) of 50% hydrogen peroxide was added over 20 minutes at about 10-12 °C. The mixture was held at about 10 °C for 2 hours and then was allowed to warm to about 19 °C over 2 hours and held at that temperature for additional 4 hours. HPLC analysis showed approximately 90% conversion of 3-aminopyridine. After cooling the reaction mixture to 10 °C, a solution of 6 g of sodium sulfite in 50 mL of water was added. To the mixture were added 50 mL of toluene and 200 g (2.5 mol) of 50% aqueous sodium hydroxide at about 25- 35 °C. Then water was added to dissolve precipitated NaCl, and the layers were separated. The organic phase was back-extracted with 45 g of 10% aqueous HCl to recover some 3-amino-2-chloropyridine in the toluene extract, and this was added back to the original aqueous phase. The combined aqueous phases were neutralized to pH 3 with

50% aqueous NaOH and extracted with toluene for 3 times. The toluene extracts were combined, washed with 30 mL of saturated aqueous NaCl, and concentrated to dryness to afford 33 g of crude 3-amino-2-chloropyridine (76% yield) with 94% purity. The product contains about 3 wt% 3-amino-2,6-dichloropyridine by HPLC assay.

EXAMPLE 3

Preparation of 3-amino-2-chloropyridine using chlorine

3-Aminopyridine (21.0 g, 0.223 mol) was added to 90 mL (ca. 108 g, 1.08 mol) of concentrated aqueous HCl (ca. 37%) in a 300-mL sidearm flask with magnetic stirring at 30-35 °C. The mixture was cooled to 15 °C (thick slurry) and chlorine gas was sparged just above the surface over about 1.5 hours at 15-20 °C. HPLC analysis showed approximately 93% conversion of 3-aminopyridine. The mixture was cooled to 10 °C and a solution of 6 g of sodium sulfite in 50 mL of water was added. To the mixture was added 30 mL of toluene and 80 g (1.0 mol) of 50% aqueous sodium hydroxide at about 25- 40 °C. Then water was added to dissolve precipitated NaCl, and the layers were separated. The aqueous phase was extracted once more with 30 mL of toluene. To the aqueous phase was added 10 g of 50% NaOH, and extracted with another 50 mL of toluene to remove 3-amino-2,6-dichloropyridine. The combined organic phase was back-extracted with 40 mL of 0.2 N aqueous HCl to recover some 3-amino-2-chloropyridine in the toluene extracts, and this was added back to the original aqueous phase. The combined aqueous phases were diluted with 100 mL of toluene and neutralized to pH 3 with about 20 g of 50% aqueous NaOH at about 35 °C. The aqueous phase was extracted with two 50-mL portions of toluene. The toluene layers were combined and washed with 20 mL of saturated aqueous NaCl. The solution was concentrated to dryness to afford 21.4 g of crude 3-amino-2-chloropyridine (74% yield) with 98.6% purity, which contained about 1.4 wt% 3-amino-2,6-dichloropyridine.

EXAMPLE 4

Preparation of 3-amino-2-chloropyridine from nicotinamide

To a 200-mL sidearm flask were charged 12.2 g (0.100 mol) of nicotinamide and 60 mL of water and the mixture was cooled to about 5 °C. Sodium hypochlorite (63 g, 11.8 wt% aqueous solution, 0.10 mol) was added to the mixture over 30 minutes at 0-5 °C along with 14 g (0.175 mol) of 50% aqueous NaOH over 30 minutes at 0-5 °C to form an *N*-chloronicotinamide solution. Meanwhile, a second flask (500-mL) was charged with 80 mL of water, which was heated to 80 °C. The *N*-chloronicotinamide solution from the first flask was then transferred to the second flask over 40 minutes, maintaining the reaction temperature at about 75-81 °C. The residue in the first flask was rinsed with 20 mL of water and the residual was also transferred to the second flask. The resulting solution was maintained at 80 °C for 15 minutes after the transfer was complete and then was cooled to 40 °C. Concentrated aqueous HCl (30 g, 37%, 0.30 mol) was added carefully at 40-50 °C to the

solution and the mixture was concentrated at a reduced pressure (ca. 50 mm Hg) until about 160 mL of water was collected. The mixture was cooled to 15 °C and anhydrous HCl (35.2 g, ca.1 mol) was added at 15 to 20 °C. The mixture was further cooled to 10 °C and 10.5 g (ca. 0.11 mol) of 32% aqueous H_2O_2 was added over 1.5 hours. After 2 hours at ambient temperature, additional 1 g of H_2O_2 was added and the mixture was held for an additional 30 minutes (ca. 93% conversion). To the mixture was added sodium bisulfite (10 mL, 30% aqueous solution), 100 mL of water, 30 mL of toluene, and 67 g of 50% aqueous NaOH sequentially at 15-25 °C. The toluene layer was separated, and the aqueous layer was washed with 30 mL of toluene. The aqueous layer was basified with 4 g of 50% aqueous NaOH to pH 3 and the product was partially extracted with toluene and then with dichloromethane. Additional product was extracted from the aqueous phase after basification to pH 7. The combined extracts were concentrated. The residue was dissolved in dichloromethane, and the resulting solution was washed with aqueous NaCl and concentrated to dryness to afford 10.4 g of 3-amino-2-chloropyridine (74% overall yield) with 95% purity.

EXAMPLE 5

Preparation of 3-amino-2-chloropyridine from nicotinamide

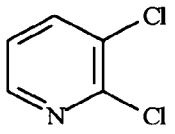
To a mixture of 24.4 g (0.200 mol) of nicotinamide and 120 mL of water at about 0 °C was added sodium hypochlorite (237 g, 6.89 wt% aqueous solution, 0.22 mol) over 30 minutes. After stirring for over 15 minutes at 0 °C, aqueous NaOH (32 g, 0.40 mol, 50 wt%) was added to the mixture over 30 minutes at 0-5 °C. This resulting solution was charged to 280 mL of water at 90 °C over 30 minutes and stirred an additional hour at 90 °C. Concentrated aqueous HCl (60 g, 37 wt%, 0.20 mol) was added over 45 minutes at 40 °C and the mixture was stirred overnight and concentrated at reduced pressure to remove most of the water. The mixture was then filtered to remove salt, which was washed with two 80-mL portions of 9% aqueous HCl. Analysis of the filtrate showed that it contained about 16.1 g of 3-aminopyridine (ca. 86% yield). To the crude 3-aminopyridine solution was added anhydrous HCl (ca. 80 g, 2.2 mol) at 0 °C. Hydrogen peroxide (17.6 g, 46% solution, 0.24 mol) was added over 2 hours at 0-5 °C, and the mixture was stirred at 15-20 °C for an additional 3 hours. To the mixture was added aqueous sodium bisulfite solution (12 mL, 30%), water (200 mL), toluene (50 mL), and aqueous NaOH (82 g, 1.03 mol, 50%) sequentially at about 0-20 °C. The layers were separated. The aqueous layer was washed with ten 50-mL portions of toluene to remove overchlorinated products, and then basified to pH 10 with 20 g of 50% aqueous NaOH. The basified aqueous solution was extracted with four 100-mL portions of toluene and the combined toluene extracts were washed with two 40-mL portions of 18 wt% aqueous HCl. HPLC analysis of the resulting aqueous HCl extracts showed it contained about 15.3 g (0.119 mol) of 3-amino-2-chloropyridine (ca.

69.7% yield from 3-aminopyridine, 60% from nicotinamide). These extracts were cooled to about -5 °C and a solution of 8.3 g of sodium nitrite (0.12 mol) in 16.6 mL of water was added over 30 minutes at about -5 to 0 °C. The resulting mixture was charged over 1 hour to a mixture containing cupric chloride dehydrate (10.14 g, 0.0595 mol), concentrated aqueous HCl (24.3 mL) and 1-chlorobutane (72 mL) at about 60 °C under a nitrogen atmosphere. After an additional 30 minutes at 60 °C, the mixture was cooled to ambient temperature and diluted with 120 mL of water. The layers were separated. The aqueous layer was extracted with two 70-mL portions of 1-chlorobutane. The combined extracts were found to contain about 14.7 g of 2,3-dichloropyridine (83.6% yield from 3-amino-2-chloropyridine, or 50% from nicotinamide).

CLAIMS

What is claimed is:

1. A method for preparing 2,3-dichloropyridine **1**,



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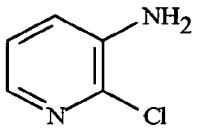
comprising the steps of:

(1) contacting a solution comprising 3-amino-2-chloropyridine **2**



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with a first aqueous solution comprising hydrochloric acid to form 3-amino-2-chloropyridine hydrochloric acid salt;

(2) contacting the 3-amino-2-chlorpyridine hydrochloric acid salt with an aqueous solution comprising a nitrite salt to form a diazonium salt; and

(3) contacting the diazonium salt with an aqueous solution comprising a Cu(II) salt in the presence of a second aqueous solution comprising hydrochloric acid, optionally in the presence of an organic solvent, to form 2,3-dichloropyridine **1**.

2. The method of Claim 1 wherein the nitrite salt is sodium nitrite.

3. The method of Claim 1 wherein the Cu(II) salt is copper(II) chloride or copper(II) oxide.

4. The method of Claim 1 wherein

the nominal mole ratio of the nitrite salt to 3-amino-2-chloropyridine hydrochloric acid salt is about 0.95 to about 2.0;

the nominal mole ratio of the Cu(II) salt to 3-amino-2-chloropyridine is about 0.05 to about 2.0;

the nominal mole ratio of hydrochloric acid in the first aqueous solution to 3-amino-2-chloropyridine is about 3 to about 10; and

the nominal mole ratio of hydrochloric acid in the second aqueous solution to 3-amino-2-chloropyridine is about 0 to about 10.

5. The method of Claim 4 wherein

the nominal mole ratio of the nitrite salt to 3-amino-2-chloropyridine hydrochloric acid salt is from 0.95 to 1.1;

the nominal mole ratio of Cu(II) to 3-amino-2-chloropyridine is from 0.2 to 0.6;

the nominal mole ratio of the hydrochloric acid in the first aqueous solution to 3-amino-2-chloropyridine is from 3 to 6; and

the nominal mole ratio of the hydrochloric acid in the second aqueous solution to 3-amino-2-chloropyridine is from 1 to 5.

6. The method of Claim 1 wherein

steps (1) and (2) are conducted at a temperature ranging from about –15 to about 20 °C; and

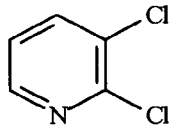
step (3) is conducted at a temperature ranging from about 30 to about 90 °C.

7. The method of Claim 6 wherein

the temperature of steps (1) and (2) range from about –10 to about 10 °C; and

the temperature of step (3) ranges from about 50 to about 80 °C.

8. A method for preparing 2,3-dichloropyridine **1**,



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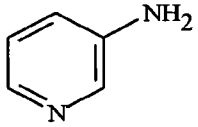
comprising the steps of:

(a) contacting a solution comprising 3-aminopyridine **3**



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with aqueous hydrochloric acid and a chlorinating agent to form a mixture;

(b) isolating a solution comprising 3-amino-2-chloropyridine hydrochloric acid salt from the mixture; and

(c) using the solution comprising 3-amino-2-chloropyridine hydrochloric acid salt in the method of Claim 1.

9. The method of Claim 8 wherein the chlorinating agent is chlorine, an alkali metal hypochlorite or a mixture of hydrochloric acid and hydrogen peroxide.

10. The method of Claim 9 wherein the chlorinating agent is chlorine or a mixture of hydrochloric acid and hydrogen peroxide.

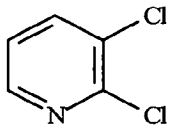
11. The method of Claim 8 wherein
the nominal mole ratio of hydrochloric acid to 3-aminopyridine is about 3 to about 20; and
the nominal mole ratio of the chlorinating agent to 3-aminopyridine is from about 0.6 to about 1.5.

12. The method of Claim 11 wherein
the nominal mole ratio of hydrochloric acid to 3-aminopyridine is about 5 to about 15; and
the nominal mole ratio of the chlorinating agent to 3-aminopyridine is about 0.8 to about 1.2.

13. The method of Claim 8 wherein the temperature of step (a) ranges from about 0 to about 60 °C.

14. The method of Claim 13 wherein the temperature of step (a) ranges from about 10 to about 35 °C.

15. A method for preparing 2,3-dichloropyridine **1**,



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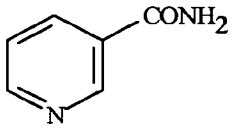
comprising the steps of:

(i) contacting nicotinamide **4**



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with a strong base and a halogenating agent in an aqueous solution at a temperature ranging from about –5 to about 20 °C to form a mixture comprising an *N*-halonicotinamide salt;

(ii) contacting the *N*-halonicotinamide salt mixture generated in step (i) with water and maintaining a resulting aqueous mixture at a temperature ranging from about 65 to about 100 °C;

(iii) isolating a solution comprising 3-aminopyridine hydrochloric acid salt from the aqueous mixture of step (ii); and

(iv) using the solution comprising 3-aminopyridine hydrochloric acid salt in the method of Claim 8.

16. The method of Claim 15 wherein the strong base is alkali metal hydroxide.

17. The method of Claim 16 wherein the alkali metal hydroxide is sodium hydroxide.

18. The method of Claim 15 wherein the halogenating agent is chlorine, bromine, or sodium hypochlorite.

19. The method of Claim 15 wherein
the nominal mole ratio of the strong base to nicotinamide is about 2 to about 5; and
the nominal mole ratio of the halogenating agent to nicotinamide is from about 0.8 to about 2.0.

20. The method of Claim 19 wherein
the nominal mole ratio of the strong base to nicotinamide is about 2 to about 3; and
the nominal mole ratio of halogenating agent to nicotinamide is about 0.9 to about 1.1.

21. The method of Claim 15 wherein
the temperature of step (i) ranges from about 0 to about10 °C; and
the temperature of step (ii) ranges from about 70 to about 95 °C.

TITLE

PROCESS FOR THE MANUFACTURE OF 2,3-DICHLOROPYRIDINE

ABSTRACT OF THE DISCLOSURE

A method for preparing 2,3-dichloropyridine is disclosed in which 3-amino-2-chloropyridine is contacted with an alkali metal nitrite in the presence of aqueous hydrochloric acid to form a diazonium salt; and the diazonium salt is subsequently decomposed by using a Cu(II) salt as a catalyst.